REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-10, 12, 14, 15 and 17-30 were pending in this application when last examined.

Claims 29 and 30 were examined on the merits and stand rejected.

Claims 1-10, 12, 14, 15 and 17-28 were withdrawn as non-elected subject matter.

Claim 29 has been amended to recite "comprises administering to a patient in need thereof" and "in an effective amount to treat said condition." Support can be found in the disclosure, for example, at page 19, line 21 to page 20, line 11, page 24, line 23 to page 25, line 30 (Example), page 36, lines 14-27, and the claim as filed.

Claim 29 has been amended to recite "condition wherein hormonal dysregulation[[,]] or hyperinsulinaemia ~~and/or~~ and insulin resistance are present." Support can be found in the disclosure, as page 30, lines 15-17. The original Abstract also refers to "autoimmune diseases and other conditions where hormonal dysregulation, hyperinsulinaemia and insulin resistance are involved".

Claim 29 has been amended to clarify the antibody binding properties along the lines of claim 1 of US 6,689,359 (which is the patent to the parent application), a copy of which is attached hereto. Support can be found in the instant disclosure, for example, at page 39, line 21 to page 40, line8 and page 40, line 8 to page 41, line 15.

Claim 30 has been amended to include a comma at line 4 between "cancer" and "cancer cachexia." Support can be found in the claim as filed.

No new matter has been added

Claims 1-10, 12, 14, 15 and 17-30 are pending upon entry of this amendment

II. INDEFINITENESS REJECTIONS

Claims 29-30 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth in item 2, parts A-E, on pages 3 and 4.

This rejection is respectfully traversed as applied to the amended claims.

Claim 29 has been amended to require administering the antibody to a patient "in need thereof" to overcome part A of the rejection.

Claim 29 has also been amended to require administering the antibody in an "effective amount to treat said condition" to overcome part B of the rejection.

Applicant respectfully traverses the rejection of claim 30 in part C. It appears that the Office is improperly equating claim breadth with indefiniteness. However, it is well settled that claim breadth is not to be equated with indefiniteness. See M.P.E.P. § 2173.04. In this regard, claim 30 should not be rejected for indefiniteness, even if not all autoimmune diseases, cancers, and cardiovascular diseases can be classified as diseases where hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present.

Furthermore, the Office appears to regard the scope of claim 30 to include diseases that do not present hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance. However, this interpretation is incorrect, because claim 30 depends on claim 29. As such, the condition in claim 30 must be a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present" as required by claim 29.

Claim 30 has been amended to include a comma at line 4 between "cancer" and "cancer cachexia" to overcome part D of the rejection.

In part E of the rejection, the Office alleges that claim 30 is indefinite for the terms "pre-IDDM" and "pre-NIDDM" on the basis that they are not defined in the Specification.

In reply thereto, it is well settled that the test for definiteness is whether those skilled in the art would understand what is claimed when the claim is read in light of the Specification. See M.P.E.P. § 2173.02. In this regard, the definiteness of claim language must be analyzed, not

in a vacuum, but in light of (1) the content of the disclosure; (2) the teachings of the art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See M.P.E.P. § 2173.02.

In our Preliminary Amendment and Response to Restriction of March 16, 2006, Applicant argued that given the discussion of the development of diabetes in the Specification at pages 4, lines 22-25; page 5, line 25; page 6, line 2; page 8, lines 7-13; and page 25, lines 22-23, the skilled artisan would understand the meaning of "pre-IDDM" and "pre-NIDDM". These arguments are reiterated herein.

Applicant remains firmly of the opinion that the skilled artisan, upon reading the disclosure and in view of the knowledge in the art, would readily understand what is meant by the terms "pre-IDDM" and "pre-NIDDM", such that an explicit formal definition in the Specification is not required.

First, the skilled artisan would be fully aware that "IDDM" is an abbreviation for "insulin dependent diabetes mellitus" (or "Type 1" diabetes). For example, that abbreviation is used at page 3, lines 23-24 of the PCT pamphlet attached herewith.

Similarly, the skilled person would be fully aware that "NIDDM" is an abbreviation for "non insulin dependent diabetes mellitus" (or "Type 2" diabetes). For example, that abbreviation is used at page 3, line 21 of the PCT pamphlet.

Second, as noted above, the instant application provides detailed information on IDDM and NIDDM (e.g. at page 4, line 3 to page 8, line 13), which makes it clear that those conditions do not normally suddenly occur in a patient, but are the result of longer-term disease processes, which may occur over a period of several years. This is also a concept with which the skilled person would be familiar.

For example, in relation to IDDM, the application refers to "preclinical diabetes" (page 4, line 9), "the immunological attack resulting in IDDM" (page 4, line 10), the "onset" of IDDM (page 4, lines 13, 14 and 28), patients who "became diabetic 1-28 months after testing" (page 5,

line 15). Also, the term "prediabetic" is used at various locations throughout the disclosure (see, for instance, page 5, lines 26, 28 and 29). The application also refers to an "underlying metabolic disorder" that exists "before the onset of diabetes" (page 6, lines 1-2). Similarly, in relation to NIDDM, the application refers to "development of NIDDM" (page 7, line 27) and reveals that "ß cell dysfunction rather than insulin resistance is the major factor predisposing to NIDDM" (page 7, lines 28-29).

Indeed, the whole point of the application is that the development of pathogenic autoantibodies is "the major factor in the diabetogenic process" (page 8, line 27). Accordingly, the antibodies and antibody fragments of the present invention can be used in both "prophylactic and therapeutic interventions of autoimmune and related diseases including IDDM and NIDDM" (page 9, lines 3-4).

Thus, it would be immediately evident to a skilled person who had read the Specification that "pre-IDDM" and "pre-NIDDM" are the underlying metabolic disorders that precede clinical IDDM and NIDDM, and which can be treated using the "prophylactic and therapeutic interventions" disclosed in the application (e.g., the types of intervention described at page 36, line 13 to page 17, line 4).

Third, "pre-IDDM" and "pre-NIDDM" are terms commonly used by those skilled in the art, as illustrated by the attached abstracts for:

(1) Rodriguez-Villar et al. (1997);

(2) Dozio et al. (1997);

(3) Suehiro et al. (2005);

(4) Bergman et al. (1997); and

(5) Standl E. (1995).

These attachments are further evidence that the terms "pre-IDDM" and "pre-NIDDM" would be clear to a person skilled in the art, even before reading the instant Specification.

In light of the above, it is respectfully submitted that the terms "pre-IDDM" and "pre-NIDDM" are clear and definite. For these reasons, the112, second paragraph, indefiniteness rejection is untenable and should be withdrawn.

In addition, kindly note that "pre-IDDM" and "pre-NIDDM" are encompassed by the term "pre-diabetes", which is clearly defined in the disclosure. Pre-diabetes is a commonly used term in the art, which encompasses both pre-IDDM and pre-NIDDM. Pre-diabetes is an asymptomatic condition which involves blood glucose levels that are higher than normal but not yet high enough to be diagnosed as diabetes. For example, the American Diabetes Association web-site explains that pre-diabetes is diagnosed in patients displaying an abnormal blood glucose response during the oral glucose tolerance test (OGTT), indicative of impaired glucose tolerance (IGT). Please see the attached copy of the discussion at http://www.diabetes.org/pre-diabetes/pre-diabetes-symptoms.jsp).

Accordingly, the term "pre-diabetes" would also be immediately clear to the skilled person.

Also, support for such can also be found in the disclosure:

(1) "preclinical diabetes" at page 4, line 9;

(2) "prediabetic individuals" page 5, line 26;

(3) "prediabetic and overtly diabetic NOD mice" at page 5, line 28;

(4) "prediabetic animals" at page 5, line 29;

(5) "prediabetic and diabetic conditions" at page 33, lines 17-19;

(6) "prediabetic condition" at page 27, line 16; and

(7) "prediabetic and diabetic states" at page 31, line 17.

Please also see Table 2 on pages 42-43, which provides the results of screening sera obtained from three prediabetic donors who subsequently became diabetic (especially, page 42, lines 3-4).

Furthermore, the application indicates that the antibodies and antibody fragments of the invention can be used "in prophylactic and therapeutic interventions of autoimminue and related diseases including IDDM and NIDDM".

Accordingly, there is abundant basis in the Specification for "pre-diabetes" (i.e., "pre-IDDM" and "pre-NIDDM") as well as clinical diabetes (i.e., "IDDM" and "NIDDM").

In the event the Office is unpersuaded with regard to the terms "pre-IDDM" and "pre-NIDDM" of claim 30, it is respectfully requested that the Office consider potential replacement language, such as "pre-diabetes" for the reasons discussed above.

Therefore, the rejection of claims 29-30 under 35 U.S.C. § 112, second paragraph, is untenable and should be withdrawn.

III. WRITTEN DESCRIPTION REJECTION

In item 4 on pages 4 and 5 of the Action, claims 29-30 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the Specification lacks written description support for (1) a method of treating a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present" and (2) a method of treating "pre-IDDM" or "pre-NIDDM". This is a new matter rejection.

This rejection is respectfully traversed as applied to the amended claims.

In part A of the rejection, the Office alleges that the Specification at page 29 discloses treating only conditions where both hyperinsulinaemia and insulin resistance are present.

In reply thereto, kindly note that claim 29 has been amended to recite "treating a condition wherein hormonal dysregulation or hyperinsulinaemia and insulin resistance are present." Support can be found in the disclosure, as page 30, lines 15-17. The original Abstract also refers to "autoimmune diseases and other conditions where hormonal dysregulation, hyperinsulinaemia and insulin resistance are involved".

Furthermore, the skilled person would understand that hyperinsulinaemia is associated with insulin resistance. For example, the Jewish Hospital Cincinnati web-site explains that "insulin resistance" is when the body's cells are resistant to insulin, and that "hyperinsulinaemia" is when the pancreas produces much more insulin than normal as a result of the insulin resistance (see the attached copy of the discussion at http://www.jewishhospitalcincinnati.com/cholesterol/insulin_resistance.htm).

Therefore, it is respectfully submitted that the amendment to claim 29 overcomes part A of the rejection.

In part B of the rejection, the Office contends "pre-IDDM" and "Pre-NIDDM" constitute new matter because the Specification does not disclose these terms. The Office notes that the words "pre-IDDM" and "pre-NIDDM" are not explicitly recited in the application..

This rejection is respectfully traversed for the same reasons set forth above in response to the 112, second paragraph, indefiniteness rejection. Again, the Applicant remains firmly of the opinion that the Specification provides adequate support for a method of treating "pre-IDDM" and "pre-NIDDM". The passages in the Specification referred to above (in relation to the indefiniteness objections) are also relevant to the instant written description rejection. In this regard, a Specification can provide explicit and implicit support for claim terminology, because a Specification discloses not only what it literally says but also what a skilled artisan would inherently understand from the disclosure.

For these reasons, the new matter rejection of claims 29-30 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

IV. ENABLEMENT REJECTION

In item 5 on pages 5-8 of the Action, claims 29-30 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the Specification lacks enablement for the claimed method.

This rejection is respectfully traversed.

The test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See M.P.E.P. § 2164.01. In fact, the test is not merely quantitative, since a considerable amount of experimentation is permissible, it if is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The Office's arguments against enablement (at pages 5-8 of the Office Action) seem to be as follows:

1. The antibody definition in claim 29 is broad, and encompasses antibodies that are not useful to treat the listed conditions (e.g. antibodies that bind to the Fc portion of an anti-TCR V antibody - the Examiner cites Dorner et al. in this regard);

2. A key aspect of the invention is the cross-reactive nature of the antibodies, yet this is not specified in claim 29;

3. The specification shows that anti-anti-TCR V antibodies can bind to pancreatic a cells and modulate insulin secretion, but there is no evidence that naturally-occurring anti-anti-TCR V antibodies play a pathogenic role across the range of listed conditions;

4. The specification discloses that anti-anti-TCR V antibodies were detected in 3 patients with IDDM, but there is no evidence that the anti-anti-TCR V antibodies play a pathogenic role in the development of IDDM in those patients;

5. The specification provides no evidence that anti-anti-TCR V antibodies can be used successfully to inhibit the pathogenic effects of naturally-occurring anti-anti-TCR V antibodies via a feedback mechanism, without themselves being pathogenic; and

6. The specification does not provide a single working example demonstrating use of an anti-anti TCR Vß antibody to treat disease.

Claim 29 has been amended to clarify binding properties of the antibody of the present invention along the lines of claim 1 of US 6,689,359 (which is the patent to the parent application). A copy of the front page and claims of this patent are attached herewith. Support for this amendment can be found in the instant disclosure, for example, at page 39, line 21 to page 40, line8 and page 40, line 8 to page 41, line 15. Accordingly, claim 29 has been amended to specify treatment with an antibody or fragment thereof with reactivity against both an anti-T cell receptor (TCR) Vβ antibody and a glycosyl phosphatidyl inositol (GPI) linkage epitope.

It is respectfully submitted that this amendment overcome at least the above-noted arguments 1 and 2 set forth in the rejection.

Furthermore, the Specification discloses that pancreas sections from normal patients "showed intraislet staining as expected" whereas "the diabetic pancreas either did not stain or stained very faintly" when tested with anti-anti-TCR Vß antibodies (page 39, line 21 to page 40, line 7). The Specification also discloses that monoclonal anti-anti-TCR Vß antibodies have a profound effect on insulin secretion by islet cells (page 40, line 8 to page 41, line 15). The Specification even discloses that the serum of pre-diabetic patients who subsequently became diabetic contains anti-anti-TCR Vß antibodies. Such data is consistent with the role of the anti-anti-TCR Vß antibodies and the centralized disease mechanism of the present invention as identified by the Applicant.

It appears that a central aspect of the Office's enablement rejection is that the Specification does not provide a single working example demonstrating use of an anti-anti TCR Vß antibody (or fragment thereof) to treat disease.

In reply thereto, Applicant respectfully argues that the underlying technical details provided in the Specification provide sufficient evidence enabling the use of the claimed antibodies and antibody fragments to treat the range of diseases specified in the claims.

In further support of this position, kindly take note of the Applicant's later related applications GB A 2429013 (published 14.02.2007) and/or WO 2007/017686 (published

15.02.2007) (both attached herewith). These later applications are effectively identical. These applications provide evidence of high levels of anti-anti-TCR Vß antibodies in newly diagnosed Type I diabetic children (see Example 3), and confirm the activity of anti-anti-TCR Vß antibodies in cancer metastasis (see Example 4). Most importantly, these applications provide clinical trial data to confirm the therapeutic utility of the claimed antibodies and antibody fragments. In particular, they provide the results of Phase I/IIa and IIb clinical trials, respectively, in which it was confirmed that antibody fragments according to the invention (in particular, CDR-derived peptides) provide long-lasting therapeutic effects in diabetic patients when analyzed using the oral glucose tolerance test (OGTT) (see Examples 6 and 7). It is respectfully submitted that the experimental data therein further confirms the effectiveness and utility of the present invention.

It also appears that Office is concerned that use of anti-anti-TCR Vß antibodies in a method of treatment might be pathogenic.

In reply thereto, please note that it is common for potentially pathogenic agents to be used in the treatment and prophylaxis of disease. For example, as explained in the instant Specification at page 25, lines 10-30, the methods of treatment of the present invention are mechanistically analogous to prior methods, which involve "administration of anti-D immunoglobulin (anti-D Ig) to Rh-negative mothers carrying Rh-positive fetuses". Clearly, when "immunizing individuals with the pathogenic antibodies" (as suggested at page 25, lines 28-30 of the Specification) an appropriate dose of the pathogenic antibody must be selected. Please see also page 36, lines 20-30 of the Specification, which provides a useful explanation of how the invention can be used to treat disease.

Finally, it is entirely reasonable for the skilled artisan to extrapolate the Applicant's findings in diabetic and pre-diabetic patients to the broad range of diseases listed in the claims. The very detailed description of various specific diseases in the application clearly establishes the links between the relevant disease and the centralized disease mechanism disclosed in this

application. In particular, it is explained how the various diseases identified by the Applicant are mediated by cross-reactive antibody binding to the "common epitope" identified by the Applicant. For example, at page 34, lines 3-14, the Specification explains how the autoantibodies of the invention will cause pleiotropic effects, because "antibodies to GPI-linked molecules have also been shown to induce cell proliferation".

Thus, the evidence that naturally-occurring cross-reactive anti-anti-TCR Vß antibodies play a pathogenic role across the range of conditions recited in the claims is provided by the Applicant's extremely detailed technical analysis of the relevant conditions, found at pages 1-8 and 24-36 of the Specification.

In view of the above, it is respectfully submitted that one skilled in the art could practice the present invention without undue experimentation based on the guidance in the Specification coupled with the knowledge in the art. In other words, the skilled artisan, upon reading the disclosure, could use the present invention without undue experimentation in method to treat a condition wherein hormonal dysregulation or hyperinsulinaemia and insulin resistance are present, by administering to a patient in need thereof an antibody or fragment thereof which specifically binds both an anti-T cell receptor (TCR) Vβ antibody and a glycosyl phosphatidyl inositol (GPI linkage epitope in an effective amount to treat said condition, optionally in conjunction with a pharmaceutically-acceptable carrier.

Therefore, the enablement rejection of claims 29-30 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

V. ANTICIPATION REJECTION

On pages 8-9 of the Action, claims 29-30 were rejected under 35 U.S.C. § 102(b) as anticipated by Howell et al. (WO 92/12996), as evidenced by Pan et al.(FASEB J., Vol. 9, pp. 43-49, 1995).

It is respectfully submitted that the present amendment overcomes this rejection.

To anticipate a claim, a cited prior art reference must teach each and every element of the claimed invention. See M.P.E.P. § 2131.01.

Pan et al. was cited merely to explain the disclosure of Howell et al. WO 92/12996, and does not itself form the basis for this rejection. The rejection is based on the alleged use of anti-anti TCR Vß antibodies in Howell et al. WO 92/12996 to treat autoimmune disease.

However, amended claim 29 calls for a method of treating a condition wherein hormonal dysregulation or hyperinsulinaemia and insulin resistance are present, which comprises administering to a patient in need thereof an antibody or fragment thereof, which specifically binds both an anti-T cell receptor (TCR) Vβ antibody and a glycosyl phosphatidyl inositol (GPI linkage epitope, in an effective amount to treat said condition, optionally in conjunction with a pharmaceutically-acceptable carrier.

Howell et al. fails to disclose or suggest an antibody or fragment thereof "with reactivity against both an anti-T cell receptor (TCR) Vβ antibody and a glycosyl phosphatidyl inositol (GPI) linkage epitope" as required in the claimed invention. Accordingly, Howell et al. fails to teach each and every element of the claimed invention. Therefore, the cited references cannot anticipate the claimed invention.

For this reason, the anticipation rejection of claims 29-30 under 35 U.S.C. § 102(b) is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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